UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/649,413	08/27/2003	Axel Ullrich	224160	5257

23460 7590 06/11/2007

LEYDIG VOIT & MAYER, LTD
TWO PRUDENTIAL PLAZA, SUITE 4900
180 NORTH STETSON AVENUE
CHICAGO, IL 60601-6731

EXAMINER	
SHAFER, SHULAMITH H	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
06/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/649,413	ULLRICH ET AL.	
	Examiner	Art Unit	
	Shulamith H. Shafer, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/2/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims

The amendment received 2 April 2007 in response to the Office Action of 31 October 2006 has been entered. Claims 7, 11 and 12 have been cancelled. Claims 1, 3 and 13 have been amended and the amendments have been entered. Claims 1, 3, 4, and 13 are pending and under consideration.

Rejections Withdrawn

The rejection of Claims 1, 3, 4, and 13 under 35 U.S.C., second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of applicant's arguments.

The rejection of Claims 1, 3, 4, and 13 under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicant's amendment to the claims.

New Rejections

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4 and 13 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Breadth of the claims: Claim 1, the independent claim of the instant invention, recites a method of treatment comprising administering to the mammal an effective amount of at least one inhibitor of the mutated FGFR-4. Thus, the claim is broadly drawn to any inhibitor of the mutated receptor without any limitations as to chemical structure or mechanism of action.

Direction/guidance in the specification: The specification teaches that the methods of the instant invention are directed toward inhibiting and/or lowering the activity of the receptor tyrosine kinase of a mutated FGFR-4 [paragraph 0010 of PGPUB 20040067885, the PGPUB of the instant application]. The specification discloses that an inhibitor is any substance which inhibits or lowers the activity of the RTK. The inhibitor can be any low-molecular weight substance directed against the RTK, a kinase-inactive receptor (any receptor which no longer has any tyrosine kinase activity) or an anti-receptor antibody [paragraphs 0017 and 0018]. The specification teaches some "Possible inhibitors are for example described in Mohammadi et al. (1997)" [0047]. However, the specification does not disclose any specific inhibitors to be used in the methods of the instant invention, nor does it provide any guidance as to the structural characteristics said inhibitor needs to have. There are no limitations in the specification as to the structure and method of action of the inhibitor. Therefore, the

specification envisions the use of any molecule, of any size, to be administered by some unspecified route. The specification discloses that point mutation at position 388, which is in the transmembrane domain, results in a constitutively signaling receptor. The receptor can be constitutively active as a homodimer, or as a heterodimer, complexed with normal receptor [paragraph 0052]. Applicant has not disclosed a mechanism by which the point mutation in the transmembrane domain renders the receptor constitutively active. Therefore, one of skill in the art would not be able to determine what type of molecule could function as an inhibitor of the mutated FGFR-4 receptor without undue experimentation.

Working examples: There are no working or prophetic examples drawn to treatment of any mammal by the methods of the instant invention.

Teachings in the art:: Zwick et al. (2002. Trends in Mol. Med 8:17-23) teach that a variety of pharmacological agents, such as monoclonal antibodies, antibody conjugates, antisense oligonucleotides and small chemical compound can be used in therapeutic strategies (to inhibit RTKs) (page 19, 2nd column, 1st paragraph and Table 1). However, the reference does not teach the use of an inactive kinase or dominant-negative receptor molecule as a method of treating carcinomas.

Mohammedi et al. (1997. Science 276:955-960, cited on IDS of 7 August 2006) discloses two compounds which inhibit the kinase activity of wild-type FGFR1. However, the reference does not teach inhibition of kinase activity in wild-type or mutated FGFR-4 receptor. Thus, one would be unable to predict that compounds of this class would inhibit an FGFR-4 wild-type or constitutively active, mutated receptor with a mutation in the transmembrane domain.

Ezzat et al. (2001. BBRC. 287:60-65) teach a soluble FGFR4 isoform that results from failure of splicing of intron 4, leading to a C-terminal truncated receptor isoform, that can functionally modulate FGF action (page 60, 2nd column, 1st paragraph). Transfection of DNA encoding sFGFR4 (soluble, truncated receptor) into NIH 3T3 cells markedly abrogated signaling in FGF-1 treated cells (page 63, 1st column, 1st paragraph). The reference teaches that truncated FGFRs that lack a tyrosine kinase domain have been shown *in vitro* to disrupt FGFR signaling by competing for ligand

binding and forming inactive heterodimers with endogenous FGFRs (page 64, 2nd column, 1st paragraph). However, there are no teachings in the art as to the effectiveness of administering truncated FGFR-4 receptors in vivo as a method of inhibiting FGF signaling, nor are there teachings in the art as to how one would ensure that the proteins would get into the cell to function as inhibitors of RTKs.

Due to the large quantity of experimentation necessary to determine what type of molecule would function as an inhibitor of a constitutively active, mutated FGFR-4 receptor, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to same, the breadth of the claims, which are drawn to treatment with any inhibitor, the complex nature of the invention, the state of the art which teaches only *in vitro* transfection of cells with DNA encoding for truncated FGFR-4 receptors as a method of inhibiting FGFR-4 signalling, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 1, 3, 4 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims recite a method of treatment comprising administration of at least one inhibitor. The claims do not disclose any limitations as to what structural characteristics the inhibitor must have. *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for

purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claim indicates that these claims are drawn to a genus, i.e., inhibitors of the mutated FGFR-4. The present claim encompasses numerous species that are not further described.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

The specification does not disclose a single species of the claimed genus or a specific molecule belonging to any of the species, but rather discloses species such as small molecules, antibodies, and kinase-inactive receptors.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, of inhibitors. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow

persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Conclusion:

Since new grounds for rejection have been raised, this action is made non-final. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SHS

EILEEN B. O'HARA
PRIMARY EXAMINER